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13. ABSTRACT *(Maximum 200 words)*

To-date 99 women have been recruited for their first assessment. All women completed the psychological assessments and 55 agreed to have their blood taken for immune assessments. The initial psychological data have been entered and preliminary results indicate that women with family histories of cancer: 1) have higher levels of general distress; 2) have higher levels of cancer-specific distress; and, 3) perceive themselves to be at higher risk for developing breast cancer, compared to women without histories of cancer in the family. To examine the relations among these variables, regression analyses were conducted. Results indicated that perceived risk for breast cancer accounted for a significant portion of the group differences in general distress, but was not directly related to general distress. On the other hand, cancer specific distress was independently related to general distress, as well as accounting for a significant portion of the group differences. These results suggest that perceived risk may contribute to the higher levels of general distress in women with family histories of breast cancer indirectly, by increasing their cancer-specific distress. Future research will examine whether the higher levels of general distress and/or cancer specific distress affect immune function in women at familial risk for breast cancer.

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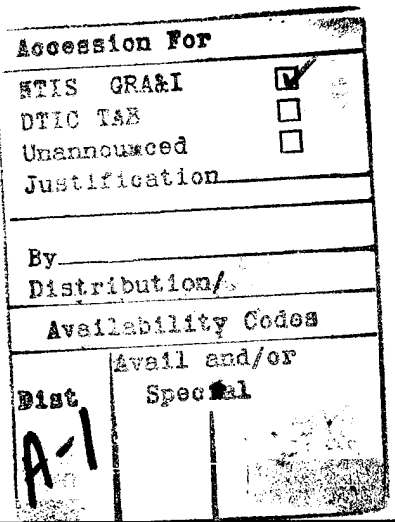

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PRELIMINARY RESULTS

Predictors of General Distress in Women at Familial Risk for Breast Cancer

INTRODUCTION

Women at familial risk for breast cancer have higher levels of general emotional distress than women at normal risk for breast cancer (Valdimarsdottir et al., 1995). Women at familial risk for breast cancer also overestimate their risk of developing breast cancer (Lerman et al.,1995) and they have high levels of cancer-specific anxiety (Kash et al., 1992; Lerman et al., 1993). Although these higher levels of perceived cancer risk and cancer-specific anxiety are likely explanations for the differences in general distress between women at familial risk and women at normal risk, this possibility has yet to be formally examined.

The present study examined the possibility that perceived risk of breast cancer may either directly contribute to the higher levels of general distress in women at familial risk of breast cancer or indirectly increase general distress by increasing their cancer-specific anxiety.

BODY

Methods:

Procedure:

Sixty-four healthy women with family histories of breast cancer (Risk Group) and thirty-five women without a family history of breast cancer (Comparison Group) participated. All of the women completed the psychological questionnaires described below.

Assessments:

Demographic Characteristics were assessed with a standard questionnaire that included information on age, race/ethnicity, education, marital status, employment, and income.

General Distress was assessed with the Brief Symptom Inventory (BSI) (Derogatis and Spencer, 1982; Derogatis and Melisaratos, 1983). The BSI assesses 9 separate symptom dimensions and provides three global indices of distress. The reliability of

the scale has been demonstrated by internal consistency (r = .77 -.90) and test -retest reliability (r = .80-.90) for all scales. The BSI was included in the present study as it has been included in previous studies of women with family histories of breast cancer (Wellisch et al., 1991a; 1991b; Kash et al., 1992). Subjects indicated how they had been feeling, "during the past week including today".

Acute Distress was assessed with the Profile of Mood States (POMS) (McNair et al., 1971). The POMS is a 65-item scale assessing six affective dimensions, whose sum provides an indication of total mood disturbance. The POMS has been found to be highly internally consistent (coefficient alpha >.87 for all subscales). Poms was included in the present study as it has been used in previous studies of women at familial risk for breast and ovarian cancer (Lerman et al., 1993; Lerman et a., 1994; Schwartz et al., 1995). Subjects indicated how they were feeling "right now."

Cancer-specific Anxiety was assessed with the Kerner cancer anxiety scale. This scale has been used in previous studies of women with family histories of breast cancer (Kash et al., 1992). Subjects indicated how they had been feeling, "during the past week including today."

Perceived Risk for Breast Cancer was assessed by instructing each participant to indicate, from 0 "not likely at all" to 100 "extremely likely", how likely she thought it was that she would develop breast cancer in her lifetime.

RESULTS

Demographic Characteristics, Perceived Risk, and Psychological Distress in Women at Familial Risk for Breast Cancer and in Women at normal Risk for Breast Cancer.

As shown in Table 1, there were no differences between the Groups on age, education, income, or ethnicity. Compared to the normal risk women, the women at familial risk for breast cancer: 1) perceived themselves to be at higher risk for developing breast cancer (p = .001); 2) had higher levels of cancer-specific anxiety (p = .01); and 3) had higher levels of general distress (p = .03).

Perceived Risk of Breast Cancer and General Distress

To examine the hypothesis that perceived risk of breast cancer contributes to the differences in general distress between women at familial risk and women at normal risk for breast cancer, a regression analysis was computed entering both Group (Risk Group and Comparison Group) and perceived risk for breast cancer into the analysis. The results revealed that: 1) after controlling for perceived risk, the relation between

Group and general distress was no longer significant ($p = .42$); and 2) after controlling for Group, higher levels of perceived risk for breast cancer were associated with significantly higher levels of general distress ($p = .034$).

These results support the hypothesis that the higher levels of general distress in women at familial risk may be due in part to their higher levels of perceived risk for breast cancer.

Perceived Risk of Breast Cancer and Cancer-Specific Anxiety

To examine the hypothesis that the higher levels of cancer-specific anxiety in the Risk Group are due to their higher levels of perceived risk for breast cancer, a regression analysis was computed entering both Group and perceived risk for breast cancer into the analysis. The results revealed that: 1) after controlling for perceived risk, the relation between Group and cancer-specific anxiety was no longer significant ($p = .32$); and 2) after controlling for Group, higher levels of perceived risk were associated with significantly higher levels of cancer-specific anxiety ($p = .002$).

These results support the hypothesis that the higher levels of cancer-specific anxiety in women at familial risk may be due in part to their higher levels of perceived risk for breast cancer.

Cancer-Specific Anxiety and General Distress

To examine the hypothesis that the higher levels of general distress in women at familial risk for breast cancer are due to their higher levels of cancer-specific anxiety, a regression analysis was computed entering both Group and cancer-specific anxiety into the analysis. The results indicated that: 1) after controlling for cancer-specific anxiety, the relation between Group and general distress was no longer significant ($p = .27$); and 2) after controlling for Group, higher levels of cancer-specific anxiety were associated with significantly higher levels of general distress ($p = .0001$).

These results support the hypothesis that the higher levels of general distress in women at familial risk for breast cancer may be due in part to their higher levels of cancer-specific anxiety.

Perceived Risk of Breast Cancer, Cancer-Specific Anxiety and General Distress

The above results suggest that the higher levels of perceived risk for breast cancer in women at familial risk contribute to their higher levels of cancer-specific anxiety; in turn the higher levels of cancer-specific anxiety in women at familial risk for breast cancer contribute to their higher levels of general distress.

To address this possibility, more directly, we conducted another regression analysis in which all three variables were included. The results (Table 2), revealed that: 1) after controlling for perceived risk and cancer-specific anxiety, the relation between Group and general distress was not significant ($p = .62$); 2) after controlling for Group and cancer-specific anxiety, the relation between perceived risk and general distress was no longer significant ($p = .27$); and 3) after controlling for Group and perceived risk, higher levels of cancer-specific anxiety were still associated with significantly higher levels of general distress ($p = .0006$).

These results support the hypothesis that perceived risk of breast cancer contributes to the higher levels of general distress in women at familial risk for breast cancer indirectly, by increasing their cancer-specific anxiety.

CONCLUSIONS

Women at familial risk for breast cancer perceived themselves to be at a higher risk for developing breast cancer than women at normal risk for breast cancer. These women also had higher levels of cancer-specific anxiety and general distress.

Higher levels of perceived risk of breast cancer may contribute to higher levels of general distress indirectly, by increasing cancer-specific anxiety.

As other studies have shown that women with family histories of breast cancer greatly overestimate their risk (Lerman and Schwartz, 1994; Lerman et al., 1995), the present results raise the possibility that effective genetic counseling may substantially reduce both cancer-specific and general distress.

Future research will examine the possibility that general distress and/or cancer-specific distress affects immune function in women at familial risk for breast cancer. Recruitment for this aspect of the research has proven more difficult than for the psychological aspect.

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Wellisch, D.K., Gritz, E.R., Schain, W., Wang, H-J., & Siau, J. (1991b) Psychological functioning of daughters of breast cancer patients: Part 2. Characterizing the distressed daughter of the breast cancer patient. Psychosomatics, 33, 171-179

TABLE 1

Demographic, Perceived Risk, and Psychological Distress Data

	Risk Group (N = 64)	Comparison Group (N = 35)
Mean Age (SEM)	45.2 (0.6)	43.3 (0.8)
Education (% > Partial College)	90%	94%
Income (% > 20 - 40 Thousand)	92%	89%
Race (% White)	89%	78%
Perceived Risk of Cancer (0% - 100% Risk) Mean (SEM)	64.3 (3.2)**	33.7 (4.0)
Mean General Distress (SEM)	0.47 (.04)*	0.32 (.04)
Mean Cancer-Specific Distress (SEM)	13.8 (0.5)*	11.2 (0.4)

** = $p < .01$ * = $p < .05$

Table 2

Regression Results for General Distress

	Standardized Regression Coefficients	Significance Levels
Group	0.05	.62
Perceived Risk of Breast Cancer	0.12	.27
Cancer-Specific Anxiety	0.35	.01

APPENDIX

1. Psychological distress in women with a familial risk of breast cancer. Published manuscript.

2. Positive and negative mood: association with natural killer cell activity. Submitted manuscript.

PSYCHO-ONCOLOGY, VOL. 4: 133–141 (1995)

PSYCHOLOGICAL DISTRESS IN WOMEN WITH A FAMILIAL RISK OF BREAST CANCER

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SUMMARY

In the present study women at familial risk for breast cancer ($N = 26$, risk group) underwent psychological assessments on two occasions: immediately prior to mammography screening and a month after notification of their normal results. Assessments included standardized measures of: acute distress; non-specific distress; intrusive thoughts; and avoidance about breast cancer. Normal risk women not undergoing mammography ($N = 27$, comparison group) completed the same measures, to provide an indication of concurrent levels of distress in women recruited from the same community. Results revealed that, prior to mammography, the risk group had high levels of acute distress, which were reduced to the level of the comparison group following notification of normal mammography results. On the other hand, despite notification of normal results, the risk group continued to have higher levels of non-specific distress, avoidance and intrusive thoughts about breast cancer. These results confirm and extend previous reports of high levels of non-specific distress and intrusive thoughts in women at familial risk for breast cancer. The findings highlight the need for further studies to determine the sources of this distress and its possible negative consequences for these individuals at risk for cancer.

The role of heredity in breast cancer has become increasingly well-recognized in the past decade (Lynch, 1990; Borresen, 1992). Healthy women who have a first-degree relative with breast cancer are two to three times more likely to develop breast cancer in their lifetimes than women without an affected first-degree relative (Anderson, 1992). The risk becomes even higher if more than one first-degree relative has been diagnosed with breast cancer and if the first-degree relative had premenopausal or bilateral breast cancer (Anderson, 1992).

Although one might expect that this increased risk for breast cancer would affect overall psychological adjustment, few studies have directly examined this possibility (Lerman and Schwartz, 1993). The importance of this issue is suggested by several studies indicating that women with higher levels of distress are less likely to practice monthly breast self-examination and are less likely to go for mammography screening (Alagna *et al.*, 1987; Lerman *et al.*, 1990, 1991, 1993; Kash *et al.*, 1992; Lerman & Schwartz, 1993).

A few clinical case reports have indicated that women with a family history of breast cancer may experience a range of adjustment difficulties (Kelly, 1983, 1987; Hyland *et al.*, 1984). Two recent larger research studies have provided data consistent with these case reports. Lerman *et al.* (1993) reported that 53% of first-degree relatives of breast cancer patients experienced intrusive thoughts about breast cancer. Kash *et al.* (1992) also found that women with a family history of breast cancer reported high levels of non-specific psychological distress on the Brief Symptom Inventory (BSI) compared to norms for that scale. On the other hand, Wellisch *et al.* (1991a), reported that daughters of women with breast cancer did not have higher levels of psychological distress on the BSI than a comparison group of women with no family history of breast cancer.

The reasons for these discrepant findings are not yet clear. One possibility is that the women

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in the study by Kash *et al.* (1992) may have been particularly distressed because they were approached for the study assessment at the time of their clinic visit for breast cancer screening. Consistent with this possibility, two previous studies of normal risk women have found that distress levels were higher on a day of breast cancer screening compared to distress levels after notification of their normal results, as little as 3 days later (Bartolucci *et al.*, 1989; Ellman *et al.*, 1989). A second possible reason for the discrepant findings is that the study of Wellisch *et al.* (1991a) compared distress levels in women at familial risk for breast cancer to those in a concurrently assessed comparison group drawn from the community, whereas the other two studies relied on historical normative data. The aims of the present study were to confirm and extend the previous findings by Kash *et al.* (1992) in two ways: (1) by comparing distress levels on the day of mammography screening (prior to notification of normal results) to distress levels a month later, a time less likely to be influenced by acute distress associated with mammography; (2) by comparing distress levels in women with family histories of breast cancer to those in women without familial risk for breast cancer and not undergoing mammography, to provide an indication of concurrent levels of distress in a comparison group drawn from the community.

Although the time course of psychological distress associated with mammography has yet to be studied, we chose to assess distress levels a month after women at familial risk received mammography screening in an attempt to reduce the possible influence of kinetic effects in this initial study. We reasoned that assessment after a shorter period, such as the 3-day interval used by Bartolucci *et al.* (1989), would be more susceptible to confounding effects, including: (1) a transient 'relief' effect associated with receiving the good news of normal mammography, which women receive on the day of screening or (2) a 'slow recovery' effect, reflecting continuing anxiety raised by the screening for breast cancer. On the other hand, assessment after a longer period would be more likely to be confounded by anticipatory distress associated with forthcoming clinical breast examinations, which are typically scheduled 6 months after mammography for women at familial risk for breast cancer.

METHODS

Subjects

Women with (risk group) and without (comparison group) a family history of breast cancer were recruited for the present study. Informed consent was obtained from all participants in accordance with a protocol approved by the institutional review boards of both Memorial Sloan-Kettering Cancer Center and Strang Cancer Prevention Clinic. All subjects were offered a modest financial incentive for participation. To limit subject heterogeneity, exclusion criteria for all subjects included: (1) non-English speaking; (2) age less than 21 years or greater than 50 years; (3) inability to provide meaningful informed consent; (4) prior or concurrent neoplasm.

The risk group of women was recruited by telephone from participants in a breast cancer surveillance clinic, previously described (Kash *et al.*, 1992). The risk group, following established guidelines (Garber *et al.*, 1991), consisted of women with two or more first-degree relatives (mother, sister, daughter) with breast cancer, a first-degree relative with premenopausal breast cancer, or a mother and a maternal grandmother with breast cancer. A total of 32 high-risk women were approached for the study and all agreed to participate. Five women failed to complete the study (citing a lack of time for the second assessment day); no differences ($p > 0.20$) were found on any study variables between this subset of women and those completing the study. To reduce extraneous sources of variability, one woman was excluded because her score on the General Severity Index (GSI) on the Brief Symptom Inventory (described below) was more than five standard deviations above the mean of all women (in both groups), including this outlier. None of the women ($N = 26$) was found to have abnormal mammogram results.

The comparison group of women was recruited by advertisements in the local community for healthy women to participate in a study of the role of emotional factors in health. These women were pre-screened for family history of breast cancer and only women with no first- or second-degree relatives with breast cancer were eligible for the study. A total of 32 women agreed to participate, and each was paired with a subject in the risk group for concurrent assessment; because five women in the

risk group did not schedule a second assessment (see above), their five paired comparison subjects were also not scheduled for a second assessment, leaving 27 women in the comparison group.

Procedures

Risk group (N = 26). Approximately 1 week before their scheduled mammography screening, the women were contacted by telephone for recruitment. The study was described as an investigation of psychological factors associated with mammography screening in women with family histories of breast cancer. Participants were scheduled to meet with study personnel on two different days: (1) on the day of their scheduled mammography; and (2) one month later. As a part of the surveillance program, all subjects were notified about their normal results on the day of the mammography. On assessment day 1, subjects completed standardized questionnaires to assess non-specific distress, intrusive thoughts and avoidance about breast cancer, and acute distress (see Psychobehavioral Measures, below) as they awaited their clinical appointments; acute distress (see below) was reassessed immediately following the notification of normal results. On assessment day 2, subjects returned to the clinic solely to meet with the research personnel. They completed the same standardized questionnaires.

Comparison group (N = 27). Interested women were contacted by telephone; the study was described as an investigation of psychological factors associated with mammography screening in women with family histories of breast cancer, in which they would serve as comparison subjects. Participants were scheduled such that on each day that a subject in the risk group was assessed, a subject in the comparison group was also assessed.

Psychobehavioral questionnaires

Subject characteristics. A standard questionnaire was used to obtain information on age, race/ethnicity, education, marital status, employment, income, and perceived lifetime cancer risk.

The Brief Symptom Inventory (BSI). The BSI (Derogatis and Spencer, 1982; Derogatis and Melisaratos, 1983), which is a brief form of the SCl-90 (Symptom Checklist-90-revised), was used to assess non-specific distress. The BSI was designed to reflect the psychological symptom patterns of psychiatric and medical patients as well as non-patient individuals. It assesses nine separate symptom dimensions (somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism), as well as providing three global indices of distress. Of particular interest was the General Severity Index (GSI), the most sensitive indicator of overall emotional distress (Derogatis and Spencer, 1982). In this sample, the coefficient alpha for the GSI was 0.93 and, for the nine symptom dimensions, the alphas ranged from a low of 0.56 for psychoticism to a high of 0.85 for depression. On both days of assessment, subjects indicated how they had been feeling 'during the past week including today'. The BSI was included in the present study because it was used in two previous studies of women with family history of breast cancer (Wellisch *et al.*, 1991a, 1991b; Kash *et al.*, 1992).

Impact of Event Scale. The IES (Horowitz *et al.*, 1979) is a 15-item self-report inventory, which assesses intrusive thoughts and avoidance. The items on the scale are anchored to a specific stressor; in this case, the threat of breast cancer. The coefficient alpha in the present sample was 0.86 for the intrusion subscale, consistent with values reported by Horowitz *et al.* (1979). On each day of assessment, subjects indicated how they had been feeling 'during the past week including today'. The intrusive thoughts subscale on the IES was of particular interest because Lerman *et al.* have reported a high incidence of intrusive thoughts in women with family histories of breast cancer (Lerman *et al.*, 1993).

Profile of Mood States (POMS). The POMS (McNair *et al.*, 1971) was used to confirm that mammography is associated with acute distress. The POMS is a 65-item scale assessing six affective dimensions (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia and confusion-bewilderment) whose sum provides an indication of total mood disturbance (distress). Consistent with previous reports (McNair *et al.*, 1971), the alpha coefficients in the present sample were high, ranging from a low of 0.75 for confusion to 0.95 for tension. On each day of assessment, subjects indicated how they were feeling 'right now'. The POMS was included in the study because it has been demonstrated to be

sensitive to acute distress under a wide range of conditions (McNair *et al.*, 1971).

Statistics

Classic analysis of variance (ANOVA) statistics on a software package, SAS (Cary, NC), were used to analyze the results. For these analyses there was one between-subject factor (group membership: risk vs comparison), and one within-subject factor (day of assessment). Simple effect analyses were computed to examine significant interactions using the overall error term as recommended by Winer (Winer, 1971). When appropriate, analysis of covariance (ANCOVA), which provides a statistical approach to control for the effects of one dependent variable on another (Keppel, 1973), was used to assess the possible contribution of psychological variables to group differences in psychological distress. Students *t* tests or Fishers exact tests were used for specific comparisons on single non-repeated dependent variables (e.g. demographics). Results indicating differences with a probability of less than or equal to 0.05 were accepted as significant.

RESULTS

Subject characteristics

Subject characteristics of the risk group and the comparison group are shown in Table 1. The majority of the women were white and well educated.

Table 1. Subject characteristics

	Groups	
	Risk	Comparison
Age[a] (years)	43.1 (0.8)	39.3 (1.6)[b]
Education (college graduate/total)	23/26	27/27
Ethnic group (white/total)	23/26	21/27
Marital status (married/total)	16/26	7/27[b]
Income (>US$40 000/total)	18/26	13/26[c]
Cancer knowledge[a]	5.1 (0.2)	4.8 (0.2)
Perceived risk for breast cancer[a,d]	59.2 (3.6)	28.1 (3.6)[b]

[a] Mean (SEM).
[b] Significant differences, $p < 0.05$; there were no other significant differences between the groups.
[c] One subject did not answer this question.
[d] Each participant was instructed to indicate, from 0 (not likely at all) to 100 (extremely likely), how likely she thought it was that she would develop breast cancer in her lifetime; mean across both assessments.

The women in the risk group were somewhat older than those in the comparison group ($p = 0.047$) and more likely to be married ($p = 0.009$). On both days of assessment, women in the risk group perceived themselves to be at higher risk of breast cancer ($p = 0.0001$). There were no other significant differences between the groups.

Acute psychological distress

As expected, mammography was associated with high levels of acute psychological distress, as

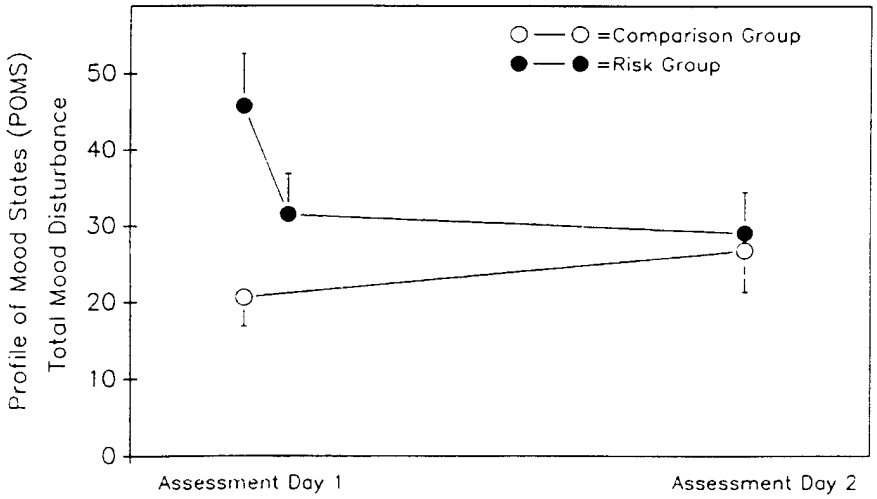

Figure 1. Increased total mood disturbance in women with a familial risk of breast cancer

assessed by the total mood disturbance score on the POMS. For the 20 women in the risk group with data on all three time-points, repeated ANOVA indicated that acute distress was significantly ($F(2, 38) = 5.9$, $p = 0.005$) higher prior to mammography (mean ± SE = 45.7 ± 6.8), compared to either immediately after receiving notification of normal results (31.5 ± 5.3) on assessment day 1, or one month later (29.11 ± 5.3).

Consistent with the within-subjects analysis above, there was also a significant interaction between day of assessment and group in repeated measures ANOVA ($F(1, 51) = 8.67$, $p = 0.004$). Simple effect analyses of the within-subject factor indicated that total mood disturbance decreased from assessment day 1 to assessment day 2 in the risk group ($p < 0.006$), but not in the comparison group ($p > 0.20$) (see Figure 1). Simple effect analyses of the between-subject factor (group)

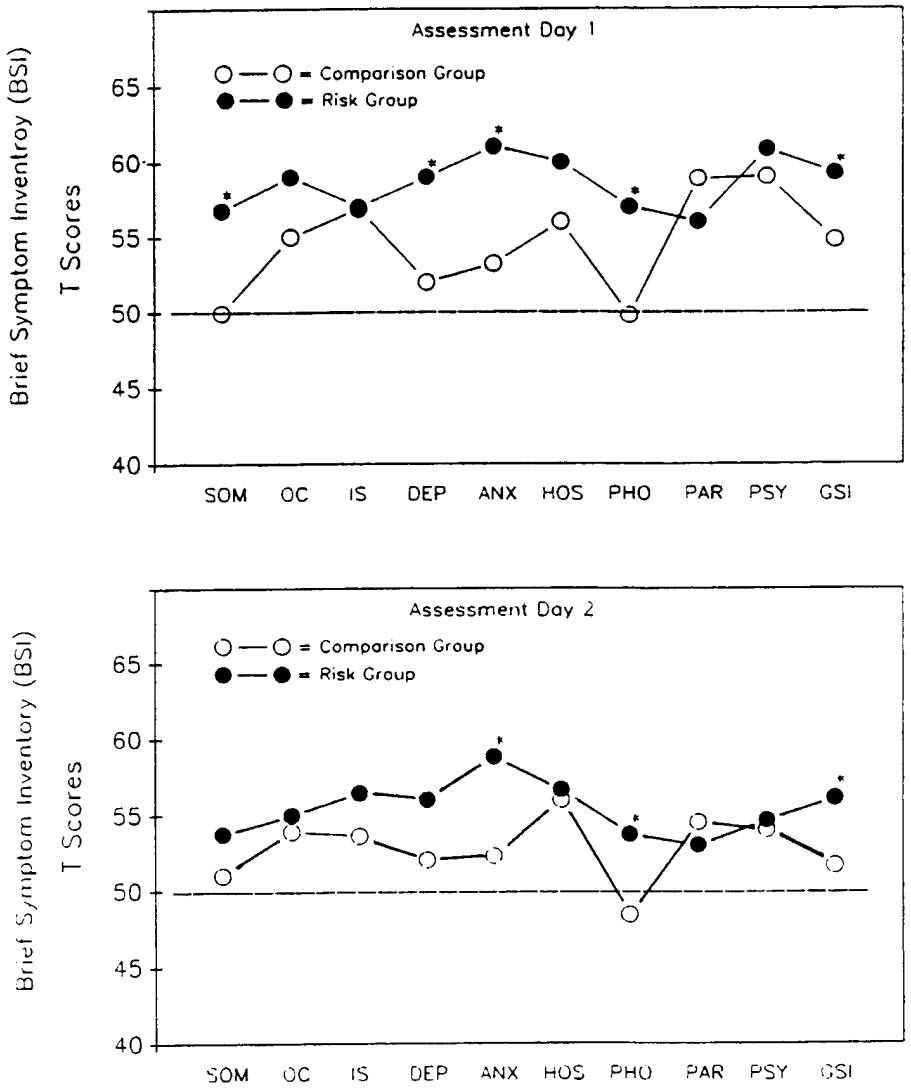

Figure 2. Increased psychological distress in women with familial risk of breast cancer. * = Significant difference, $p < 0.05$. The T-score of 50 represents norms from healthy American women (mean = 50; SD = 10). SOM, somatization; OC, obsessive compulsive; IS, interpersonal sensitivity; DEP, depression; ANX, anxiety; HOS, hostility; PHO, phobic anxiety; PAR, paranoid ideation; PSY, psychoticism; GSI = General Severity Index

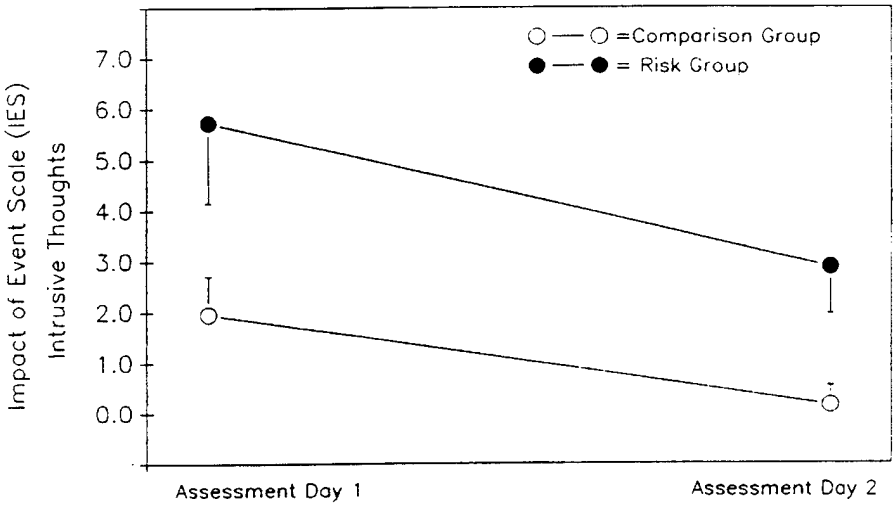

Figure 3. Increased intrusive thoughts in women with a familial risk of breast cancer

indicated that the groups differed on assessment day 1 ($p < 0.002$), but not on assessment day 2 ($p > 0.20$). The results remained significant after entering age and marital status as covariates.

Non-specific psychological distress

Non-specific psychological distress, as measured by the General Severity Index (GSI) on the BSI, was significantly higher in the risk group than in the comparison group on both days of assessment ($F(1, 51) = 4.29$, $p = 0.043$), with assessment day 2 showing lower levels of distress ($F(1, 51) = 11.45$, $p = 0.001$). The interaction term was not significant ($p > 0.20$). Entering age and marital status into the analyses as covariates did not alter the results. As shown in Figure 2, these findings indicate that women at familial risk for breast cancer had higher levels of non-specific distress than normal risk women even a month after notification of normal mammography results.

To characterize the source of the significant difference between the groups on the GSI, we conducted planned comparisons on the results of each of the nine symptom dimensions that go into the GSI score. On assessment day 1 (see Figure 2), women in the risk group had significantly higher levels of somatization ($p < 0.05$), depression ($p < 0.05$), anxiety ($p < 0.01$), and phobic anxiety ($p < 0.01$) than those in the comparison group. On assessment day 2, the risk group had significantly higher levels of anxiety ($p < 0.01$) and phobic anxiety ($p < 0.05$), but no longer had higher somatization or depression scores ($p > 0.20$). These results indicate that women at familial risk for breast cancer have higher levels of general anxiety even after notification of normal mammography.

Intrusive thoughts and avoidance

As shown in Figure 3, the risk group had higher levels of intrusive thoughts about breast cancer, as measured by the IES, than the comparison group, across both days of assessment ($F(1, 51) = 7.20$, $p = 0.009$), with assessment day 2 showing lower levels ($F(1, 51) = 11.94$, $p = 0.001$). The interaction was not significant (see Figure 3). A similar pattern of results was found for avoidant thoughts, with main effects for group ($F(1, 51) = 8.08$, $p = 0.006$) and for assessment day ($F(1, 51) = 18.22$, $p = 0.0001$). The main effect of group remained significant after entering age and marital status as covariates into these analyses. These results indicate that women at familial risk for breast cancer have higher levels of intrusive thoughts and avoidance about breast cancer even a month after notification of normal mammography.

DISCUSSION

There were two major findings in the present study. First, compared to women at normal risk for breast cancer (not undergoing mammography),

women at familial risk had higher levels of acute distress (POMS) when they were assessed immediately before mammography, but not when assessed following notification of normal results. Second, compared to the normal risk women, women at familial risk had higher levels of non-specific distress (GSI), intrusive thoughts and avoidance about breast cancer (IES) when they were assessed immediately before mammography, as well as when they were assessed 1 month after notification of normal results. In the discussion that follows we first consider each of these findings and its relation to previous reports in the literature. We then discuss potential sources of the higher levels of distress in women at familial risk of breast cancer. Finally, we consider the clinical implications of these results.

In the present study, the high levels of acute distress observed prior to mammography in women at familial risk for breast cancer (risk group) were reduced to the level of normal risk women not undergoing mammography (comparison group) immediately following notification of normal mammography results. At the assessment a month later, the risk group and comparison group continued to show no difference in acute distress. The swift and lasting reduction in acute distress following notification of normal results is consistent with previous studies of normal risk women undergoing mammography (Bartolucci *et al.*, 1989; Ellman *et al.*, 1989). Indeed, acute reductions in distress following notification of normal results have been found in a number of studies of individuals undergoing various types of diagnostic tests, including prenatal screening and genetic testing (Marteau *et al.*, 1988; Marteau, 1989; Tibben *et al.*, 1994).

On the other hand, we found that even 1 month after notification of normal mammography results, the risk group continued to have higher levels of non-specific distress (GSI), avoidance and intrusive thoughts about breast cancer (IES) than the comparison group. These findings support and extend those of Kash *et al.* (1992), who found that women at familial risk for breast cancer ($n = 122$), who were assessed around the time of a yearly mammography screening, had higher levels of distress than the norms for the BSI. The present results are not consistent with the hypothesis that the findings of Kash *et al.* (1992) were simply due to assessing subjects around the time of their mammography screening for breast cancer. It must be noted, however, that the results of the present study do not rule out the possibility that the higher levels of non-specific distress, avoidance and intrusive thoughts 1 month after mammography are due to a slow recovery from distress elicited by that life stressor. It will be necessary to conduct additional research, with multiple assessments over the months preceding and following mammography with subjects randomly selected from the community, before one can accept the hypothesis that women at familial risk are chronically more distressed than normal risk women, independent of the emotional effects of mammography.

The present study is the first conducted within the USA to report that non-specific distress, avoidance and intrusive thoughts in women at familial risk are higher than those found in a comparison group of normal risk women, concurrently recruited from the same metropolitan area. These results are at variance with those of Wellisch *et al.* (1991a), who recruited women from the community by newspaper advertisements and found no differences on the BSI between daughters of women with breast cancer and comparison women with unaffected mothers. The women at familial risk for breast cancer in the present study differed in at least two relevant aspects from those in the study by Wellisch *et al.* (1991a). First, their family histories of breast cancer were more severe (e.g., two or more affected relatives), putting them at higher risk. This higher objective risk may have resulted in higher levels of perceived risk for the women in the present study, although differences in assessment of perceived risk between the two studies preclude direct comparison. Second, the women in the risk group in the present study were self-selected participants in a breast cancer screening program, which may yield a different cohort than community sampling (Hobbs *et al.*, 1980; Taplin *et al.*, 1989). Women who have elected to participate in a surveillance program may be more distressed than women who do not participate in such programs, independent of their objective risk of breast cancer. It should be noted, however, that Lerman *et al.* (1993) found high levels of intrusive thoughts about cancer in a community sample of women with a first-degree relative with breast cancer. Additional research is needed to assess the generalizability of data collected from surveillance clinics, which are likely to be the source of subjects for initial genetic screening studies.

There are numerous possible explanations for the higher levels of distress, avoidance and intrusive thoughts in women at familial risk for breast cancer.

It is tempting to speculate that women with higher levels of objective risk for cancer, based on epidemiological data (e.g., multiple affected relatives), may perceive themselves to be at higher risk for this life-threatening disease and therefore have chronically higher levels of psychological distress. The small number of subjects in the present study precluded adequate assessment of the relations between perceived risk and psychological distress, but preliminary analyses did not reveal significant correlations (data not shown). In addition to the perceived threat of breast cancer, future studies should consider other aspects of a family history of breast cancer that may account for higher levels of distress. For example, these women may be taking care of the affected relative or experiencing bereavement following the death of a loved one. On the other hand, chronically elevated distress might have its origins in the interactions between a newly diagnosed mother and a daughter at a critical developmental stage, as suggested by Wellisch *et al.* (1991b).

There were two unexpected findings from the comparison group in the present study. First, the perceived risk of breast cancer of 28%, although significantly lower than that of the risk group, is considerably higher than the true population risk of 11%. It is not clear whether this overestimation represents a selection bias in the present study or truly reflects an overestimation of risk in the general public. Second, non-specific distress (BSI), avoidance and intrusive thoughts about breast cancer (IES) decreased in the month between the two assessments. The reasons for these reductions are not yet clear. It is possible that participation in cancer studies may initially elicit thoughts of cancer and psychological distress, which may decrease as the subjects become more familiar with research procedures. Future investigations of psychological factors in cancer research should thus include multiple days of assessment to establish stable baselines.

It is important to consider the potential clinical impact of emotional distress on individuals at risk for cancer. Regardless of the source, high levels of distress may have a number of negative consequences for individuals at risk for cancer (Lerman and Schwartz, 1993). First, distress may affect surveillance behaviors. Higher levels of general distress have been reported to reduce the likelihood that women will practice monthly breast self-examination or go for regular mammography screening (Alagna *et al.*, 1987; Lerman *et al.*, 1990, 1991, 1993; Kash *et al.*, 1992; Lerman and Schwartz, 1993). In addition, higher levels of anxiety associated with mammography may reduce the likelihood that women will go for regular screening appointments (Lerman *et al.*, 1990). Second, distress has long been known to adversely affect information and decision-making processes (Janis, 1982; Hamilton, 1982). Even a modest impairment in cognitive ability could be important for women at risk for breast cancer. These women, who are currently faced with a wealth of information concerning their risk of cancer, will soon also have difficult decisions to make regarding genetic testing and how they should respond to results (Miki *et al.*, 1994; Lerman *et al.*, 1994; Offit and Brown, 1994). These considerations indicate the importance of investigating the effectiveness of psychosocial interventions in this population, a research effort that is now ongoing.

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Positive and Negative Mood: Association with Natural Killer Cell Activity.

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ABSTRACT

Negative mood (e.g., emotional distress) has been repeatedly shown to be accompanied by alterations in immune function, but little research has addressed potential effects of positive mood. In the present study of 48 healthy women, we concurrently assessed positive and negative mood and examined their relations to natural killer (NK) cell activity, known to be particularly sensitive to psychological factors. Results indicated that positive mood was related to higher levels of NK cell activity in women who reported negative mood, but not in individuals who reported no negative mood. These results raise the possibility that positive mood may moderate, or buffer, the effects of negative mood on immune function.

Key words: psychoneuroimmunology, positive mood, negative mood, natural killer cell activity

INTRODUCTION

Individuals undergoing stressful life events have been found to have a higher incidence of a variety of illnesses that suggest immune system involvement (Brown & Harris, 1989; Holmes & David, 1989). As recently confirmed in a meta-analytic review (Herbert & Cohen, 1993) studies have consistently found altered immune function in individuals encountering various distressing life events including: loss of a spouse or loved one, divorce or marital separation, unemployment, taking care of a sick relative, and taking academic examinations. There is also evidence that undesirable day-to-day events (e.g., argument with spouse) can affect immune function (Stone, Neale, Cox, Napoli, Valdimarsdottir, & Kennedy-Moore, 1994; Stone, Marco, Cruise, Cox, & Neale, 1995). The possible effects of positive life events on immune function have received less research attention, but initial evidence suggests an association. For example, Stone and colleagues (1994) found that individuals reporting more desirable daily events (e.g., close interaction with spouse) had stronger salivary antibody responses (sIgA) to oral challenges with a novel antigen.

It has been hypothesized that the relations between life events (positive or negative) and alterations in immune function are mediated by changes in affective states which, in turn, lead to changes in neuroendocrine pathways and/or in health related behaviors (Cohen, Kessler, & Gordon, 1995). Supporting the hypothesized role of negative affective states, Stone and colleagues (1995) reported that increases in negative mood mediated the relation between undesirable daily events and lower antibody responses to an oral antigenic challenge. Several other studies have shown that negative affective states are associated with alterations in various immune parameters, including: reductions in natural killer (NK) cell activity (Irwin, Daniels, Bloom, Smith, & Weiner, 1987; Bovbjerg & Valdimarsdottir, 1993); reduced lymphocyte proliferative responses (Linn, Linn, & Jensen, 1981); lower serum antibody responses to Hepatitis B vaccine (Jabaaij, Grosheide, Heijtink,

Duivenvoorden, Ballieux, & Vingerhoets, 1993); and, reduced salivary antibody responses to oral challenges with a novel antigen (Stone, Cox, Valdimarsdottir, Jandorf & Neale, 1987).

On the other hand, relatively little research has addressed the possible influence of positive affective states on immune function. Stone and colleagues have reported that increases in positive mood mediated the relation between desirable daily events and salivary antibody responses to antigenic challenge (Stone et al., 1995). Relations between higher levels of positive mood and higher salivary antibody responses to antigenic challenges were also reported in two previous studies by this group (Stone et al., 1987; 1994).

These studies on salivary antibody responses to oral antigenic challenges raise the possibility that positive and negative mood may have differential effects on immune function. However, it is not clear if immune measures besides salivary antibody responses are similarly affected. The present study focused on the possibility that NK cell activity may be differentially affected by positive and negative mood. Considerable evidence indicates that NK cell activity is particularly sensitive to emotional distress (O'Leary, 1990) but little research attention has been paid to the possible effects of positive mood on NK cell activity.

Consistent with previous naturalistic studies, we hypothesized that negative mood would be associated with lower levels of NK cell activity, while positive mood might prove to be associated with higher levels of NK cell activity.

METHODS

Subjects:

Women were recruited by announcements posted in staff areas of three contiguous

medical centers. Participants (N = 48) reported having no chronic medical condition, no current use of medication and no symptoms of infectious disease in the last three days. The mean age was 38.8 years (range 22-63). The majority of the women were white (71%), single (71%), employed (85%), and well educated (72% had attended college).

Procedure:

Subjects were scheduled to come to the laboratory at the same time of day on two consecutive days. On the first day, basic demographic data were collected and subjects completed psychobehavioral questionnaires (see below). Blood was then collected for immune assessment (see below), conducted by a technician blind to the results of the questionnaires. On the second day of assessment, subjects again completed the psychobehavioral questionnaires and blood samples were collected.

Assessments:

Demographic information was collected on a standard questionnaire to obtain information on age, race/ethnicity, and marital status (Bovbjerg & Valdimarsdottir, 1993).

Positive and negative affect was assessed using the positive and negative mood scales established by Guadagnoli and Mor (1989). These scales were derived from principal components analyses of the 65 mood adjectives in the Profile of Mood States (McNair, Lorr, & Droppleman, 1971). The two scales (positive and negative affect) each consist of 7 adjectives scored from 0 (not at all) to 4 (extremely), with results reported as the mean of all 7 items. In two independent samples of subjects, these investigators found that the scales for positive and negative mood had high alpha coefficients ($> .70$) and were independent of each other. We confirmed these high alpha coefficients ($> .90$) within each scale in the present sample, but found that the scales were inversely correlated ($r = -.49$, $p < .01$). It should be noted that during

the course of the study the timeframe of the questionnaire was modified from "this week including today" (N = 20) to "today" (N = 28), reflecting considerations relevant to our ongoing research program. To ensure that this modification did not influence the results presented here, we entered this grouping variable as a covariate into the analyses described below; including this covariate did not alter any of the results. Because each scale was significantly correlated (p's $< .01$) across the two assessment days, the mean of the two days was computed and used in all subsequent analyses.

Daily Habits (e.g., alcohol consumption) that may be influenced by affective states, and which could in turn influence immune function (Kiecolt-Glaser & Glaser, 1988), were assessed with standard questionnaire (Bovbjerg & Valdimarsdottir, 1993). This questionnaire uses a self report format to assess: sleep, eating patterns, cigarette smoking, alcohol consumption, use of licit and illicit drugs, as well as infectious disease symptomatology, over the three days prior to the blood collection.

Natural Killer (NK) Cell Activity was assessed using peripheral blood mononuclear cells, isolated from heparinized blood samples by standard Ficoll-Hypaque gradient centrifugation (Bovbjerg & Valdimarsdottir, 1993). Cytotoxic activity against the classic NK-sensitive K562 tumor cell line was assessed in a standard ^{51}Cr release assay (Bovbjerg & Valdimarsdottir, 1993). Data from all effector to target cell ratios were included in the statistical analyses, as a more conservative approach than use of summary values such as lytic units (Pollock, Zimmerman, & Fuchshuber, 1990). Because the NK data collected on both days was significantly correlated (p's $< .01$), the mean was computed and used in all subsequent analyses.

RESULTS

Positive and negative mood.

The mean level of negative mood in the study sample was 0.42 ± 0.90 (SD). Consistent with previous studies (Watson and Tellegen, 1985) the negative mood

scores were highly skewed towards the low end (22 of the 48 subjects had negative mood scores of zero). The mean level of positive mood was 2.3 $\pm$ 0.85. Again consistent with previous studies (Watson and Tellegen, 1985), the positive mood scores were approximately normally distributed. Because of these different distributions, negative mood was treated as a dichotomous variable (women with some negative mood vs women with no negative mood) and positive mood was treated as a continuous variable in all subsequent analyses.

Association between NK cell activity and affective states.

The hypothesis that negative and positive mood would be differentially associated with NK cell activity was examined with multivariate regression analyses (using SAS General Linear Model). Because of the inverse correlation between the mood scales (see Methods) positive mood, negative mood, and their interaction were entered into the analysis. The results indicated that positive mood was associated with higher levels of NK cell activity ($F(1,44) = 10.01$, $p = .002$) and negative mood was associated with lower levels of NK cell activity ($F(1,44) = 7.35$, $p = .009$) mood. The interaction between positive mood and negative mood was also significant ($F(1,44) = 8.05$, $p = .007$), across the three effector to target cell ratios.

To determine the source of the significant interaction, we examined the relations between positive mood and NK cell activity within the subgroups of women who report no negative mood (N = 22) and those reporting some negative mood (N = 26). As shown by the flat regression line in the Figure, higher levels of positive mood were not associated with higher levels of NK cell activity in the subgroup of women who reported no negative mood. In terms of statistics, regression with repeated measures revealed no significant relation to NK cell activity, ($F(1,20) = .06$, $p = .80$).

On the other hand, as shown by the upward slope of the regression line in the Figure, higher levels of positive mood were associated with higher levels of NK cell activity

in the subgroup of women reporting some negative mood. Among these women reporting some negative mood, positive mood accounted for 41% of the variance in NK cell activity ($F(1,24) = 16.86$, $p < .001$). To rule out the possible contribution of variability in negative mood to NK cell activity in this subgroup, we entered negative mood as a covariate into the analysis; positive mood remained a significant predictor of NK cell activity ($F(1,23) = 15.92$, $p < .001$).

Do differences in demographic variables and/or health behaviors account for the relations between NK cell activity and affective states?

To examine the possibility that individual differences in demographic variables or daily habits (e.g., amount of sleep) may have accounted for the results presented above, we examined the relations between these variables and NK cell activity in this sample. The results indicated that none of the demographic or health behaviors were related to NK cell activity, except age (which was associated with NK cell activity at one effector to target cell ratio). However, entering age as a covariate into the analyses above did not alter the results. In addition, the absence of a relation between positive mood and NK cell activity in the subgroup of women reporting no negative mood could not be attributed to lower variability in positive mood in this subgroup of women (p's > .20).

DISCUSSION

The results of the present study revealed that the interaction of positive and negative mood was significantly related to NK cell activity. Women who reported having negative mood, but little positive mood had the lowest levels of NK cell activity. Higher levels of positive mood (among the women reporting negative mood) were associated with levels of NK cell activity similar to those seen in women reporting no negative mood. On the other hand, among those women reporting no negative mood, we found no further increase in NK cell activity associated with higher levels of

positive mood. These results raise the possibility that positive mood may serve as a buffer, reducing the effects of negative mood on NK cell activity.

The possibility that positive emotions may serve as a stress buffer has been suggested by several investigators (Edwards and Cooper, 1988; Lazarus, 1991; Lazarus, Kanner, & Folkman, 1980). For example, Lazarus and colleagues (1980; 1991) have articulated three possible means by which positive emotions may serve as buffers. Positive emotions may: 1) enhance coping by providing a "breather" from ongoing stress; 2) help to sustain ongoing coping needed to resolve a challenge; or, 3) restore psychological resources depleted by stress. Empirical support for the stress buffering effects of positive mood is scant. Consistent with the hypothesis, Cohen and Hoberman (1983) have reported that the number of positive events experienced by an individual moderated the relation between negative life-events and depressive/physical symptomatology.

To our knowledge, the present study is the first to consider the possible role of positive mood as a buffer, interacting with the effects of negative mood, on measures of immune function. Previous studies of affective states and immune function have focused on the direct effects of positive and negative mood. For example, Stone and colleagues (1987, 1984) found that negative mood was associated with smaller antibody responses to challenge antigen, while positive mood was associated with larger antibody responses. These studies, however, did not examine possible interactions, making comparisons to the results of present study problematic.
It is also difficult to compare the results of the present study to those of two recent studies in which positive and negative moods were experimentally induced (Knapp, Levy, Giorgh, Black, & Fox, 1992; Futterman, Kemeny, Shapiro, & Fahey, 1994). Knapp and colleagues (1992) found no significant changes in NK cell activity following the induction of maximally disturbing or maximally pleasurable emotional experiences. Futterman and colleagues (1994) found transient increases in the levels of NK cell activity following the induction of either positive or negative mood states by "method"

acting techniques. Neither of these studies was designed to examine the possible buffering effect of positive mood. It would be of interest in future studies to experimentally test the buffering effects of positive mood, perhaps following methods analogous to those of Gerin and colleagues, who have recently experimentally demonstrated the buffering effects of social support on cardiovascular reactivity Gerin, Milner, Chawla, & Pickering, 1995).

The results of the present naturalistic study should be considered preliminary for several reasons. First, the study sample was relatively modest in size and was restricted to women. Second, study measures of mood and immune function were limited. Third, we can not rule out the possibility that the observed relations between mood and NK cell activity may have been secondary to a number of unassessed psychosocial mediating variables. For example, individuals with more social support have been reported to have higher levels of positive mood (Cohen & Wills, 1985), and independent studies have found that social support is associated with higher NK cell activity (Baron, Cutrona, Hicklin, Russell, & Lubaroff, 1990). Positive mood may also be related to humor, which has been reported to have effects on immune function (Lefcourt, Davidson-Katz, & Kueneman, 1990; Edwards & Cooper, 1988; Martin & Dobbin, 1988; Dillon, Minchoff, & Baker, 1985). Fourth, differences in positive and negative emotions may reflect underlying personality differences. For example, several studies have found that negative mood is strongly related to neuroticism whereas positive mood is related to extraversion (Costa & McCrae, 1980). Based on the present results, further research with a larger sample of both men and women, with additional measures, assessed at multiple time points is clearly warranted. The initial evidence from the present study, consistent with the buffering hypothesis, of positive mood highlights the importance of further research in this area.

It remains to be determined whether the influence of positive mood on immune function will predominantly be due to effects on putative neuroendocrine pathways and/or more indirect influences having an impact on coping mechanisms (Brown,

Sirota, Niaura, & Engebretson, 1993; Edwards & Cooper, 1988). Regardless of the mechanisms responsible, the present study suggests that the assessment of positive mood may make an important contribution to future studies of psychological influences on immune function.

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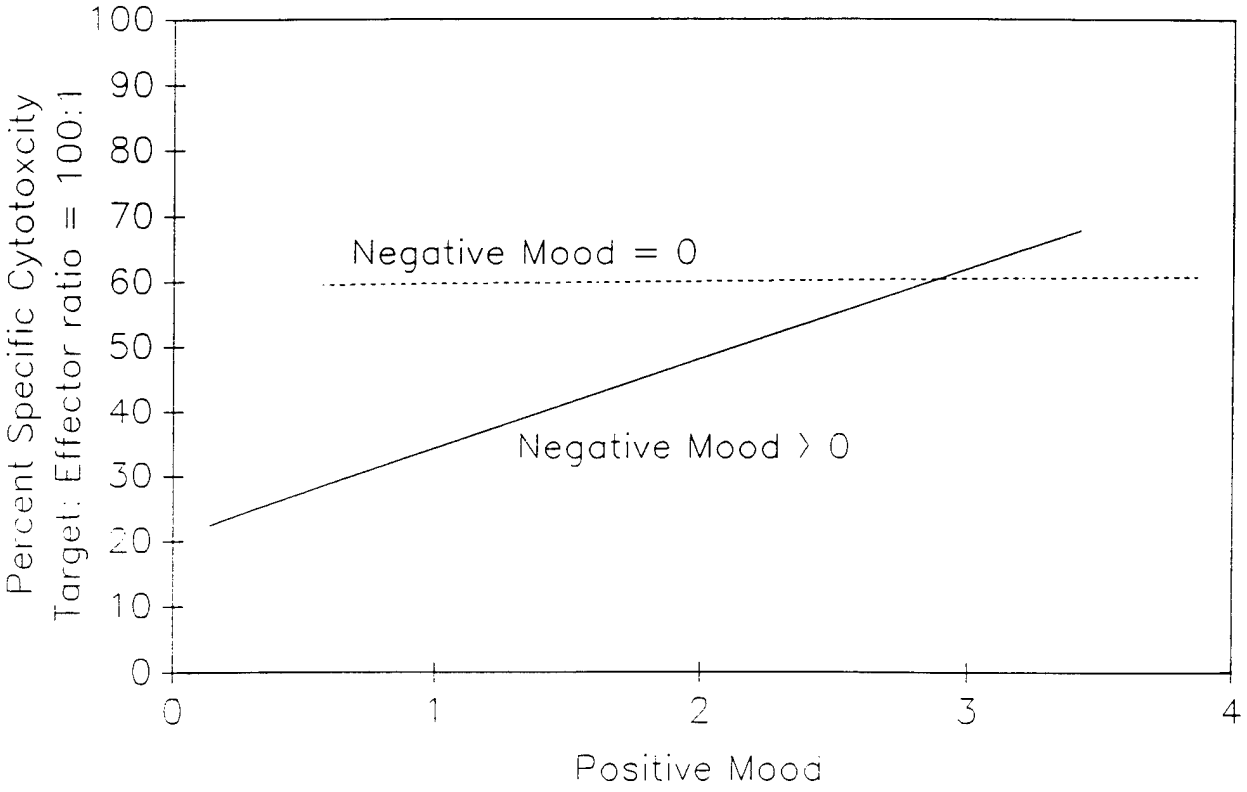
Figure Legend

Figure 1. Relations between positive mood and NK cell activity in groups of women with (solid line) and without (dotted line) negative mood.


Percent Specific Cytotoxcity
Target: Effector ratio = 100:1
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Negative Mood = 0
Negative Mood > 0
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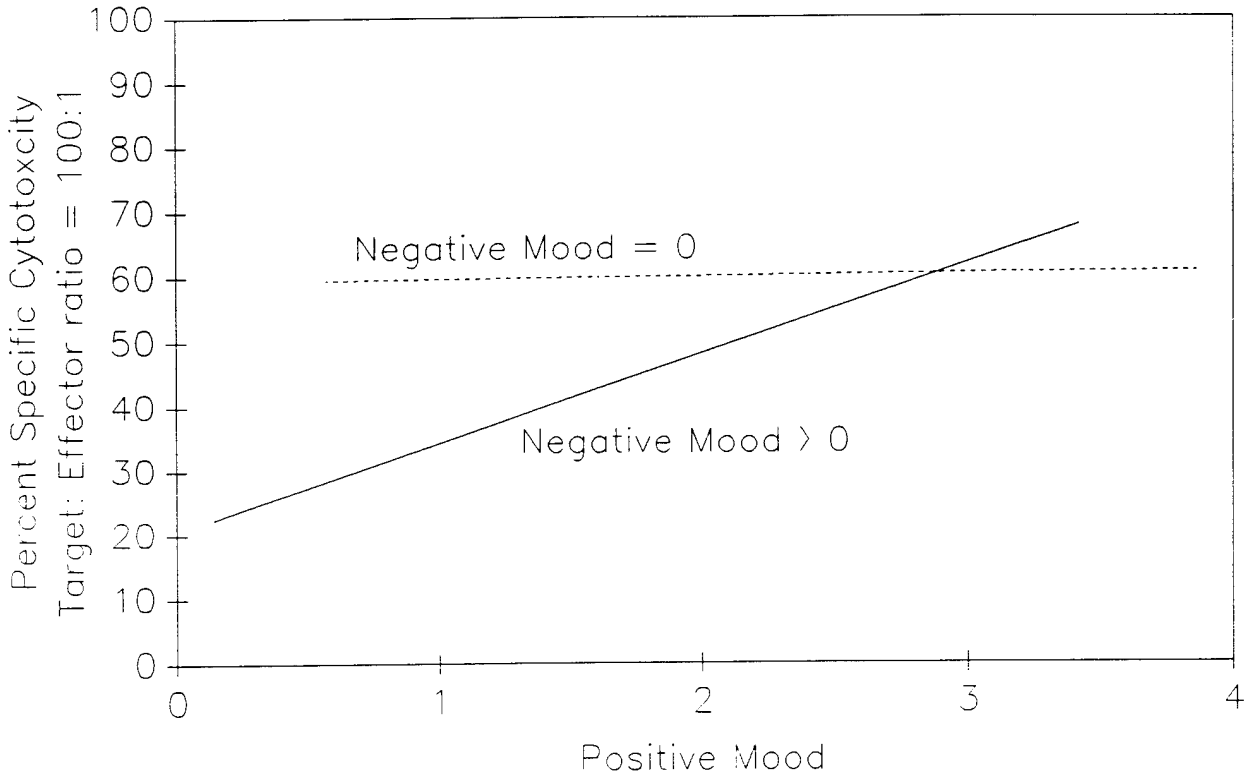
Positive Mood


Percent Specific Cytotoxcity
Target: Effector ratio = 100:1
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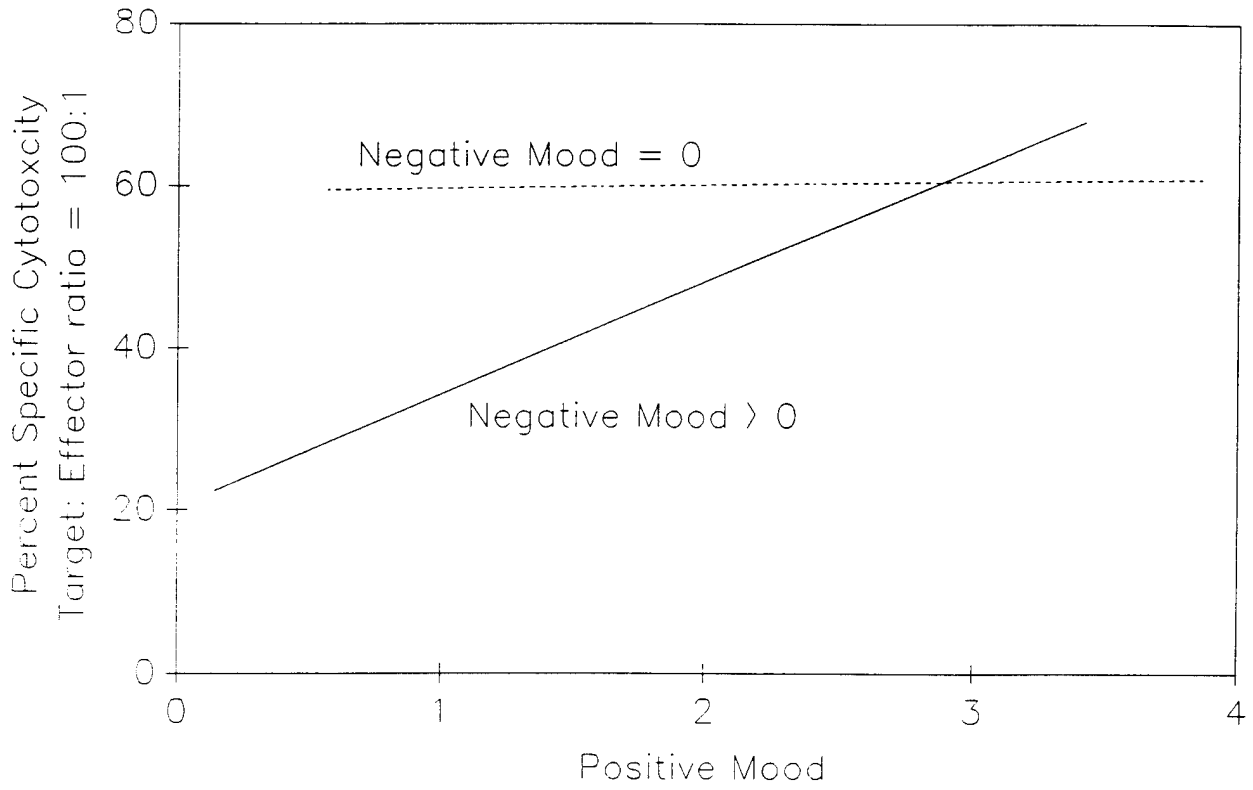
Negative Mood = 0
Negative Mood > 0
Positive Mood


Percent Specific Cytotoxcity
Target: Effector ratio = 100:1
80
60
40
20
0
Negative Mood = 0
Negative Mood > 0
0
1
2
3
4
Positive Mood